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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/398,405	09/16/99	SALERNO J	JCS96-01Z

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DAVID E BROOK ESQ
HAMILTON BROOK SMITH & REYNOLDS PC
TWO MILITIA DRIVE
LEXINGTON MA 02173

EXAMINER	
UNGAR, S	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 06/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/398,405	Salerno
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *one* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 23, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☐ Claim(s) _____ is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-59* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

1. The election filed April 23, 2001 (Paper No.8) in response to the Office Action of December 19, 2000 (Paper No. 6) is acknowledged and has been entered.

2. Upon review and reconsideration and in view of Applicant's comments, the restriction requirement of December 19, 2000 is vacated and the following substituted. It is noted that the number of inventive groups has been reduced from 83 to 57 and that new Groups 34 or 35 appear to encompass Applicant's elected Group 32. Claims 1-59 are pending in the application and are currently under prosecution.

2. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

Group 1. Claims 1-3 and 6-11 are drawn to an agent that specifically inhibits a constitutive endothelial nitric oxide synthase classified in Class 530, subclass 300+.

Group 2. Claims 1, 2, 4, 12-15 are drawn to an agent that specifically inhibits constitutive neuronal nitric oxide synthase classified in Class 530, subclass 300+. Claims 12-15 will be examined as they are drawn to the invention of Group

Group 3. Claims 1 and 5 are drawn to an agent that specifically inhibits inducible nitric oxide synthase, classified in Class 530, subclass 300+.

Group 4. Claims 16-18 are drawn to an activator of endothelial nitric oxide synthase wherein the activator is an antibody, classified in Class 530, subclass 387.1.

Group 5. Claims 16 and 19 are drawn to an activator of constitutive endothelial nitric oxide synthase wherein the activator is an peptide, classified in Class 530, subclass 3300+.

Group 6-11. Claim 19 is drawn to a constitutive neuronal nitric oxide synthase activator peptide wherein the peptide is SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, respectively, classified in Class 424, subclass 133.1. Applicant is required to elect a single Group (sequence) for examination. It is noted that Examiner requested clarification of whether or not the peptides claimed are activators of constitutive NNOS. Clarification has not been made. Thus, in order to facilitate compact prosecution, claim 19 has been included both with claim 16 drawn to endothelial nitric oxide synthase and as a group alone drawn to neuronal nitric oxide synthase.

Group 12. Claims 20-22 are drawn to an activator of neuronal nitric oxide synthase which antagonizes autoinhibition classified in Class 530, subclass 387.1

Group 13-21. Claims 23-24 are drawn to an antibody which binds to an amino acid sequence wherein the amino acid sequence is SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, classified in Class 530, subclass 387.1. Applicant is required to elect a single Group (sequence) for examination.

Group 22-31. Claim 25 is drawn to a nucleic acid encoding an antibody that binds to SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, classified in Class 530, subclass 387.1. Applicant is required to elect a single Group (sequence) for examination.

Group 32. Claims 26-27 and 29-30 are drawn to a method of inhibiting endothelial nitric oxide synthase, classified in Class 514, subclass 2.

Group 33. Claims 26 and 28 are drawn to a method of inhibiting neuronal nitric oxide synthase, classified in Class 514, subclass 2.

Group 34. Claims 31 and 48 are drawn to a method of activating endothelial nitric oxide synthase wherein the activator is an antibody, drawn to treating a disease comprising administering an antibody activator, classified in Class 424, subclass 130.1.

Group 35. Claims 31-32 and 49 are drawn to a method of activating endothelial nitric oxide synthase wherein the activator is a peptide, drawn to treating a disease comprising administering a peptide, classified in Class 514, subclass 2.

Group 36. Claims 33 and 50 are drawn to a method of activating neuronal nitric oxide synthase, treating a disease, classified in Class 514, subclass 2.

Group 37. Claims 34-37 are drawn to an agent that inhibits inducible nitric oxide synthase by blocking electron transfer from NADPH to an active site, classified in Class 514, subclass 2.

Groups 38-39. Claim 38 is drawn to an activator of endothelial nitric oxide synthase which binds to one or more amino acids in SEQ ID NO:21, SEQ ID NO:24, respectively, classified in Class 514, subclass 2. Each invention will be examined as it is drawn to the respective elected group.

Groups 40-42. Claim 39 is drawn to an activator of inducible nitric oxide synthase which binds to one or more amino acids in sequence of SEQ ID NO:2, SEQ ID NO:22, SEQ ID NO:25, respectively, classified in Class 514, subclass 2. Each invention will be examined as it is drawn to the respective elective Group.

Group 43. Claims 40-41 are drawn to an antibody that inhibits inducible nitric oxide synthase, classified in Class 530, subclass 387.1.

Group 44. Claims 40 and 42 are drawn to an antibody that activates inducible nitric oxide synthase, classified in Class 530, subclass 387.1.

Group 45. Claims 43 and 45-47 are drawn to a method of treating a disease comprising administering an inhibitor of endothelial nitric oxide synthase, classified in Class 514, subclass 2. Claims 45-47 will be examined as they are drawn to the elected Group.

Group 46. Claims 44-47 is drawn to a method of treating a disease comprising administering an inhibitor of neuronal nitric oxide synthase, classified in Class 514, subclass 2. Claims 45-47 will be examined as they are drawn to the elected Group.

Group 47. Claims 51-53 are drawn to a method of identifying an agent that inhibits activity of by modulation of calmodulin activation of nitric oxide synthase, classified in Class 435, subclass 4.

Group 48. Claims 54-55 are drawn to a method of identifying an agent that activates activity of nitric oxide synthase by modulation of autoinhibition, classified in Class 435, subclass 4.

Group 49. Claim 56 is drawn to a method of identifying an agent that blocks electron transfer from NADPH to an active site of the nitric oxide synthase, classified in Class 435, subclass 4.

Group 50. Claim 57 is drawn to a nucleic acid sequence encoding the peptide of claim 6, classified in Class 536, subclass 23.1.

Group 51. Claim 58 is drawn to a nucleic acid sequence encoding the peptide of claim 12, classified in Class 536, subclass 23.1.

Groups 52-57. Claim 59 is drawn to a nucleic acid sequence encoding SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, respectively, classified in Class 536, subclass 23.1. Each invention will be examined as it is drawn to the respective elective Group.

3. The inventions are distinct, each from the other because of the following reasons:

Inventions 1-31, 37-44 and 50-57 as disclosed are biologically and chemically distinct, unrelated in structure and function, made by and used in different methods and are therefore distinct inventions.

Inventions 32-36 and 45-49 are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

The inventions of Groups 1/45 and 32 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the inhibitor product as claimed can be used in a materially different process such as affinity chromatography.

The inventions of Groups 2/46 and 33 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the inhibitor product as claimed can be used in a materially different process such as affinity chromatography.

The inventions of Groups 4 and 34 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the

instant case the antibody product as claimed can be used in a materially different process such as affinity chromatography.

The inventions of Groups 5/38/39 and 35 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the activator product as claimed can be used in a materially different process such as affinity chromatography.

The inventions of Groups 6-12 and 36 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the activator product as claimed can be used in a materially different process such as affinity chromatography.

The inventions of Groups 1-3/37 and 47 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the inhibitor product as claimed can be used in a materially different process such as affinity chromatography.

The inventions of Groups 4-12/38/39 and 48 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the activator product as claimed can be used in a materially different process such as affinity chromatography.

The inventions of Group 1 and 33-36/46/448-49 are not at all related because the product of Group 1 is not used in any of the methods of Groups 33-36/46/448-49.

The inventions of Group 2 and 32/34-36/45/48-49 are not at all related because the product of Group 2 is not used in any of the methods of Groups 32/34-36/45/48-49.

The inventions of Group 3 and 32-36/45-46/48-49 are not at all related because the product of Group 3 is not used in any of the methods of Groups 32-36/45-46/48-49.

The inventions of Group 4 and 32-33/35-36/45-47/49 are not at all related because the product of Group 4 is not used in any of the methods of Groups 32-33/35-36/45-47/49.

The inventions of Group 5 and 32-34/36/45-47/49 are not at all related because the product of Group 5 is not used in any of the methods of Groups 32-34/36/45-47/49.

The inventions of Groups 6-12 and 32-35/45-47/49 are not at all related because the products of Groups 6-12 are not used in any of the methods of Groups 32-35/45-47/49.

The invention of Groups 13-21/ 40-44 and 32-36/45-49 do not appear to be at all related because the products of Groups 13-21/40-44 do not appear to be used in any of the methods of Groups 32-36/45-49.

The inventions of Groups 23-31/50-57 and 32-36/45-49 are not at all related because the products of Groups 23-31/20-27 are not used in any of the methods of Groups 32-36/45-49.

The inventions of Groups 37 and 32-36/45-46/48-49 are not at all related because the products of Group 37 is not used in any of the methods of Groups 32-36/45-46/48-49.

The inventions of Groups 38-39 and 32-34/36/45-47/49 are not at all related because the products of Groups 38-39 are not used in any of the methods of Groups 32-34/36/45-47/49.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, restriction for examination purposes as indicated is proper.

5. Group 1 is further subject to election of a single disclosed species.

Claims 6 is generic to a plurality of disclosed patentably distinct species comprising peptides with different structures and therefore different functions wherein the peptides are (a) SEQ ID NO:9 (claim 7), (b) SEQ ID NO:1 (claim 8), ©

SEQ ID NO:12 (claim 11), (d) SEQ ID NO:13 (claim 11), (e) SEQ ID NO:14 (claim 11), (f) SEQ ID NO:15 (claim 11).

6. Group 2 is further subject to election of a single disclosed species.

Claims 12 is generic to a plurality of disclosed patentably distinct species comprising peptides with different structures and therefore different functions wherein the peptides are (a) SEQ ID NO:2 (claims 12 and 15), (b) SEQ ID NO:16 (claim 14), © SEQ ID NO:17 (claim 14), (d) SEQ ID NO:18 (claim 14), (e) SEQ ID NO:19 (claim 14).

7. Group 5 is further subject to election of a single disclosed species.

Claims 16 and 19 are generic to a plurality of disclosed patentably distinct species comprising peptides with different structures and functions wherein the peptides are (a) SEQ ID NO:4, (b) SEQ ID NO:5, © SEQ ID NO:6, (d) SEQ ID NO:7, (e) SEQ ID NO:8, (f) SEQ ID NO:9.

8. Group 26 is further subject to election of a single disclosed species.

Claims 21 and 32 are generic to a plurality of disclosed patentably distinct species comprising peptides with different structures and functions wherein the peptides are (a) SEQ ID NO:4, (b) SEQ ID NO:5, © SEQ ID NO:6, (d) SEQ ID NO:7, (e) SEQ ID NO:8, (f) SEQ ID NO:9.

9. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable

over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

10. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

12. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

13. Applicant's traversal of the vacated restriction requirement is relevant to the instant restriction requirement. In the interests of compact prosecution, Examiner responds to the traversal as follows:

Applicant argues that claim 16 is drawn to an activator of endothelial nitric oxide synthase which is a class of agents and includes the antibodies of claims 17 and 18 as well as the peptides of claim 19. Applicant further requests that the antibody and peptide claims be examined together and that they this examination will not pose a burdensome search on the examiner. The argument has been considered but has not been found persuasive because it is clear from a review of the claims and Applicant's arguments that claim 16 is an improper implied Markush group. MPEP 2173.05(h) provides that the materials set forth in a Markush group ordinarily must belong to a recognized physical class or chemical class or to an art-recognized class. Antibodies and peptides have both different structures and functions and are made by and used in separate methods are do not belong to a recongized physical class, chemical class or an art recognized class..Thus, the claim 16 has been included in two groups, one drawn to an antibody and the other drawn to the peptides. Further, as drawn to the burdensome nature of the search, the inventions are classified differently, necessitating different searches in the US Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

Applicant further argues that the Commissioner has decided that, in most cases, up to ten (10) independent and distinct nucleotide sequences will be examined in a single application without restriction. The argument has been noted

but has not been found persuasive because the language of the statement is "up to ten". Search of a single sequence is included in this group. Further, MPEP 803.04 specifically states that "normally ten sequences constitute a reasonable number for examination". MPEP further goes on to state that "In some exceptional cases, the complex nature of the claimed material.....may necessitate that the reasonable number of sequences to be selected be less than ten". In the instant case, the complex nature of the claimed material requires that only one sequence be searched due to the limitations of the huge databases required to be searched for even a single sequence. Search of more than one sequence places an undue burden on the Office.

Applicant further argues that since Claims 16 and 19 are drawn to activators of endothelial nitric oxide synthase, they should be rejoined with the methods, since search of the antibody and peptide with the method claims will not by unduly burdensome. The argument has been considered but has not been found persuasive for the reasons previously set forth and further for the reasons set forth above.

Applicant further requests reconsideration in light of the exceptional burden the restriction requirement places upon the Applicant. The argument has been considered and upon review and reconsideration the restriction requirement has been redrawn. However, as drawn to the 57 remaining groups, 35 USC 101 specifically states that **a** patent may be obtained for any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof (emphasis added).

14. **Please Note:** In an effort to enhance communication with our customers and reduce processing time, Group 1640 is running a Fax Response Pilot for Written

Restriction Requirements. A dedicated Fax machine is in place to receive your responses. The Fax number is 703-308-4135. A Fax cover sheet is attached to this Office Action for your convenience. We encourage your participation in this Pilot program. If you have any questions or suggestions please contact Anthony Caputa, Ph.D., Supervisory Patent Examiner at 703-308-3995. Thank you in advance for allowing us to enhance our customer service. Please limit the use of this dedicated Fax number to responses to Written Restrictions.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 1, 2001